A phase I trial investigating the Aurora B kinase inhibitor BI 811283 in combination with cytarabine in patients with acute myeloid leukaemia

Authors

Hartmut Döhner,[1] Carsten Müller-Tidow,[2*] Michael Lübbert,[3] Walter Fiedler,[4] Alwin Krämer,[5] Jörg Westermann,[6] Gesine Bug,[7] Richard F. Schlenk,[1†] Utz Krug,[2‡] Rainer-Georg Goeldner,[8] James Hilbert,[9§] Tillmann Taube[10] and Oliver G. Ottmann[11¶]

Affiliations

[1]Department of Internal Medicine III, University of Ulm, Ulm, Germany; [2]Department of Medicine A, University Hospital Muenster, Muenster, Germany; [3]Department of Hematology, Oncology and Stem Cell Transplantation, University of Freiburg Medical Center, Faculty of Medicine, Freiburg, Germany; [4]Department of Medicine II, University Medical Center Hamburg-Eppendorf, Hamburg, Germany; [5]Department of Internal Medicine V, University of Heidelberg and German Cancer Research Center (DKFZ), Heidelberg, Germany; [6]Medizinische Klinik mit Schwerpunkt Hämatologie, Onkologie und Tumorimmunologie, Charité – Universitaetsmedizin Berlin, Berlin, Germany; [7]Department of Medicine, Hematology/Oncology, Goethe University, Frankfurt/Main, Germany; [8]Biostatistics and Data Sciences, Boehringer Ingelheim International GmbH, Biberach, Germany; [9]Clinical Pharmacokinetics/Pharmacodynamics, Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT, USA; [10]Medical Oncology, Boehringer Ingelheim International GmbH, Biberach, Germany; [11]Department of Medicine, Hematology/Oncology, Goethe University, Frankfurt/Main, Germany

*Current affiliation: Department of Medicine V, Heidelberg University Hospital, Heidelberg, Germany

[†]Current affiliation: NCT Trial Center, National Center for Tumor Diseases (NCT), Heidelberg, Germany

[‡]Current affiliation: Department of Medicine 3, Krankenhaus Leverkusen, Leverkusen, Germany

[§]Current affiliation: Applied Biomath, LLC, Winchester, MA, USA

[¶]Current affiliation: Department of Haematology, School of Medicine, Cardiff University, Cardiff, UK

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Contact information for correspondence:
Hartmut Döhner
Department of Internal Medicine III
University of Ulm
Albert-Einstein-Allee 25
Ulm, Germany

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BI 811283, an adenosine triphosphate-competitive, reversible and potent inhibitor of Aurora B kinase, has demonstrated antitumor activity in acute myeloid leukaemia (AML) cell lines (Gürtler *et al*, 2010a; Gürtler *et al*, 2010b; Mross *et al*, 2016; Tontsch-Grunt *et al*, 2010). Here we report a phase I trial that evaluated the maximum tolerated dose (MTD), safety, efficacy and pharmacokinetics (PK) of BI 811283 with low-dose cytarabine (LDAC) in patients with AML considered ineligible for intensive treatment (NCT00632749).

Patients with previously untreated (except hydroxyurea) or relapsed/refractory AML (excluding acute promyelocytic leukaemia) considered unsuitable for intensive induction or salvage therapy were randomized to one of two schedules, combining BI 811283 (24-hour intravenous infusion; 4-week cycle) with LDAC (20 mg twice daily subcutaneously; days 1–10 of a 4-week cycle). In Schedule A, patients received BI 811283 on days 1 and 15. In Schedule B, patients received BI 811283 on day 1. BI 811283 dose escalation followed a 3+3 design (BI 811283 starting dose: 5 mg).

The primary endpoint was to determine the MTD of the two BI 811283 schedules in combination with LDAC based on the incidence of DLTs. Further endpoints included: incidence and intensity of AEs, response, PK of cytarabine with BI 811283. Full methodological details are in the Supporting Information. All patients provided written informed consent. The trial was registered at ClinicalTrials.gov (NCT00632749).

Of 68 randomised patients, 64 were treated; (Schedule A, n=28; Schedule B, n=36). At baseline (Table SI), 11 (17·2%), 37 (57·8%) and 16 (25·0%) patients had an Eastern Cooperative Oncology Group (ECOG) score of 0, 1 and 2, respectively. Median age was 73 (range, 49–89) years. Forty-four patients (68·8%) were previously untreated for AML and 20 (31·3%) patients had relapsed/refractory disease. Twenty-two patients (34·4%) had adverse-

risk genetics, two patients (3·1%) had favourable-risk genetics, and 20 (31·3%) and six patients (9·4%) had intermediate-risk I and II genetics, respectively.

Dose escalations and DLTs are shown in Table I. In Schedule A, DLTs were seen in the 120 mg dose group; the BI 811283 dose was therefore de-escalated to 100 mg and a further three patients were enrolled. As no DLTs were seen at the 100 mg dose level, the MTD in Schedule A was determined to be 100 mg. In Schedule B, the BI 811283 dose was escalated to 420 mg without the MTD being reached. Due to a strategic decision by the sponsor to halt development of BI 811283, recruitment was stopped at the 420 mg dose.

All treated patients had at least one AE during study participation. The most common AEs reported in Schedule A were anaemia (53·6%), nausea (50·0%) and pyrexia, febrile neutropenia and leukopenia (each 39·3%), and in Schedule B were pyrexia (52·8%), thrombocytopenia (50·0%) and anaemia and nausea (each 47·2%). Grade ≥3 AEs occurring in >10% of patients in a treatment group are shown by system organ class in Table II and incidence of AEs by dose in Table SII.

Overall, 82·8% of patients had AEs that were considered drug related by the investigators. AEs that led to discontinuation were reported in 39·3% of patients in Schedule A and 25·0% of patients in Schedule B. A total of 26 patients (40·6%) had fatal AEs (10 patients [35·7%] in Schedule A and 16 [44·4%] in Schedule B), mainly due to infections and AML progression; only one death (neutropenic sepsis in an 82-year-old female) was considered related to trial medication.

The median number of courses completed was 1 (range, 0–3) with Schedule A and 1 (range, 0–15) with Schedule B. The median number of courses was 2 (range, 1–15) for patients with previously untreated AML and 1 (range, 1–6) for patients with relapsed/refractory AML.

Best overall response is presented in Table SIII. In Schedule A, two patients (7·1%) achieved a complete remission (CR); 10 patients (35·7%) had no change as their best response, 11 (39·3%) had progressive disease and for five patients (17·9%) no response assessment was available. In Schedule B, five patients (13.9%) achieved a CR. Additionally, one patient (2·8%) had a CR with incomplete haematologic recovery (CRi) and one further patient (2·8%) had a partial remission (PR). Seventeen remaining patients (47·2%) had no change, eight patients (22·2%) had progressive disease and for four patients (11·1%) no response assessment was available. In Schedule A, both patients who achieved CR had previously untreated AML, and in Schedule B, all but one patient who achieved CR, CRi or PR had previously untreated AML. No dose-related trend in response rate was observed and responses occurred after a median of 1 cycle of therapy (range, 1–7). For the eight patients overall who had a best response of CR or CRi, the median remission duration was 263 days (range, 15–1492).

BI 811283 plasma PK profiles suggested no effect of the dosing schedule on the PK of BI 811283, and in both treatment schedules, suggested close to dose-proportional PK (Fig S1). Cytarabine plasma concentration profiles were similar in each BI 811283 dose group (Fig S2) and the PK parameters of cytarabine did not vary with BI 811283 dose (data not shown), indicating that cytarabine PK was not influenced by BI 811283.

In summary, this phase I trial demonstrated an acceptable safety profile with BI 811283 administered at two different treatment schedules in combination with LDAC. Other Aurora kinase inhibitors, including the Aurora B kinase inhibitor barasertib, have demonstrated encouraging activity as both monotherapy and in combination, in phase I/II trials in patients with AML (Bavetsias and Linardopoulos 2015). However, the results of this study do not indicate improved anti-leukaemic activity of BI 811283 in combination with LDAC compared with

historical results for LDAC alone. The clinical development of BI 811283 was stopped for strategic reasons, but it has been hypothesized that Aurora kinase inhibition in combination with inhibition of other key oncogenic drivers in AML (e.g., FMS-like tyrosine kinase receptor-3) may provide improved outcomes and impede tumour resistance. Therefore, further clinical exploration of Aurora B kinase as a therapeutic target in AML might be warranted.

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Authorship contributions

HD designed the study, analysed and interpreted the data, and provided study materials and patient data. CM-T, ML, WF, AK, JW, GB, RFS and OGO collected and assembled data. UK collected and assembled data, and provided study materials and patient data. RGG designed the study, assembled data, and analysed and interpreted the data. JH and TT designed the study, and analysed and interpreted the data. All authors contributed towards the writing and approval of the manuscript for submission.

Disclosure of conflicts of interests

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GSO, Jazz Pharma and Teva; research funding from Pfizer; and has acted in an advisory role for Ariad/Incyte. AK has received support for work outside the submitted work from Bayer, Merck and Teva. JW has received honoraria, research funding and travel expenses from Amgen, Bristol-Myers Squibb, Celgene, Daiichi Sankyo and Novartis. GB has received honoraria from Boehringer Ingelheim. RFS has received support for work outside the submitted work from Boehringer Ingelheim, Celgene, Novartis, Pfizer and Teva. UK reports receiving research funding from Boehringer Ingelheim; lecture fees from Celgene and Jazz Pharma; and has participated in advisory boards for Boehringer Ingelheim, Celgene, Gilead Sciences and Roche. R-GG and TT are employees of Boehringer Ingelheim. JH was an employee of Boehringer Ingelheim at the time of study conduct and is currently an employee of Applied Biomath, LLC. All other authors declare no potential conflicts of interest.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Data S1. Methods.

Table SI. Patient demographic and baseline disease characteristics.

Table SII. Incidence of AEs by dose.

Table SIII. Best overall response.

Fig S1. Geometric mean plasma concentration–time profiles of BI 811283 during and after the 24-hour infusion of BI 811283. (A) Day 1, cycle 1, Schedule A. (B) Day 15, cycle 1, Schedule A. (C) Day 1, cycle 1, Schedule B.

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Tables

Table I. DLTs in cycle 1 and for determination of MTD.

BI 811283 dose level	Patients entered*, *n*	Patients with DLT, *n*	DLTs
Schedule A			
5 mg	4	0	–
15 mg	3	0	–
30 mg	3	0	–
60 mg	4	0	–
100 mg	7	0	–
120 mg	7	2	Grade 3 tumour lysis syndrome (*n* = 1), grade 3 acute renal failure (*n* = 1)
Schedule B			
5 mg	4	1	Grade 3 folliculitis (in the context of treatment-emergent neutropenia)
40 mg	4	0	–
80 mg	5	0	–
160 mg	3	0	–
240 mg	7	1	Grade 3 increased transaminases
300 mg	4	0	–
360 mg	3	1	Grade 4 hyperuricaemia
420 mg	6	0	–

DLT, dose-limiting toxicity; MTD, maximum tolerated dose.

*According to protocol, patients who were not evaluable for DLT (did not complete at least 1 cycle for reasons other than DLT) were replaced for determination of the MTD. Therefore, the patient number in some dose groups is different from three or six. Fourteen treated patients did not complete the first treatment cycle for reasons other than DLT (most commonly due to early progression or non-DLT AEs) and were therefore replaced for determination of the MTD.

Table II. AEs grade ≥3 occurring by system organ class in >10% of patients (both schedules, all doses, irrespective of relationship to trial drug) with preferred term displayed if reported in ≥2 patients in a treatment group.

System organ class* *Preferred term*	Schedule A (days 1 and 15 of 4-week cycle) *n* = 28				Schedule B (day 1 of 4-week cycle) *n* = 36				Total *N* = 64
	CTCAE grade 3	CTCAE grade 4	CTCAE grade 5	CTCAE grade 3–5	CTCAE grade 3	CTCAE grade 4	CTCAE grade 5	CTCAE grade 3–5	CTCAE grade 3–5
Blood and lymphatic system disorders	5 (17·9)	16 (57·1)	0	21 (75·0)	6 (16·7)	22 (61·1)	0	28 (77·8)	49 (76·6)
Anaemia	11 (39·3)	1 (3·6)	0	12 (42·9)	9 (25·0)	2 (5·6)	0	11 (30·6)	23 (35·9)
Febrile neutropenia	9 (32·1)	1 (3·6)	0	10 (35·7)	14 (38·9)	0	0	14 (38·9)	24 (37·5)
Leukocytosis	2 (7·1)	1 (3·6)	0	3 (10·7)	0	0	0	0	3 (4·7)
Leukopenia	1 (3·6)	9 (32·1)	0	10 (35·7)	2 (5·6)	12 (33·3)	0	14 (38·9)	24 (37·5)
Neutropenia	0	2 (7·1)	0	2 (7·1)	0	8 (22·2)	0	8 (22·2)	10 (15·6)
Thrombocytopenia	0	9 (32·1)	0	9 (32·1)	2 (5·6)	16 (44·4)	0	18 (50·0)	27 (42·2)
Infections and infestations	9 (32·1)	0	5 (17·9)	14 (50·0)	11 (30·6)	1 (2·8)	9 (25·0)	21 (58·3)	35 (54·7)
Infection	2 (7·1)	0	0	2 (7·1)	1 (2·8)	0	0	1 (2·8)	3 (4·7)
Pneumonia	7 (25·0)	0	2 (7·1)	9 (32·1)	5 (13·9)	1 (2·8)	3 (8·3)	9 (25·0)	18 (28·1)
Pneumonia fungal	2 (7·1)	0	0	2 (7·1)	2 (5·6)	0	0	2 (5·6)	4 (6·3)
Sepsis	1 (3·6)	0	1 (3·6)	2 (7·1)	0	0	4 (11·1)	4 (11·1)	6 (9·4)
Neoplasms benign, malignant and unspecified	0	0	1 (3·6)	1 (3·6)	1 (2·8)	1 (2·8)	4 (11·1)	6 (16·7)	7 (10·9)
Neoplasm malignant	0	0	1 (3·6)	1 (3·6)	0	1 (2·8)	4 (11·1)	5 (13·9)	6 (9·4)
Metabolism and nutrition disorders	5 (17·9)	0	0	5 (17·9)	3 (8·3)	2 (5·6)	0	5 (13·9)	10 (15·6)

Hyperglycaemia	2 (7·1)	0	0	2 (7·1)	0	0	0	0	2 (3·1)
Hypokalaemia	0	0	0	0	2 (5·6)	1 (2·8)	0	3 (8·3)	3 (4·7)
Tumour lysis syndrome	3 (10·7)	0	0	3 (10·7)	1 (2·8)	0	0	1 (2·8)	4 (6·3)
Nervous system disorders	3 (10·7)	1 (3·6)	0	4 (14·3)	3 (8·3)	1 (2·8)	0	4 (11·1)	8 (12·5)
Dizziness	2 (7·1)	0	0	2 (7·1)	0	0	0	0	2 (3·1)
Syncope	0	0	0	0	2 (5·6)	0	0	2 (5·6)	2 (3·1)
Cardiac disorders	2 (7·1)	0	1 (3·6)	3 (10·7)	2 (5·6)	0	0	2 (5·6)	5 (7·8)
Acute myocardial infarction	0	0	0	0	2 (5·6)	0	0	2 (5·6)	2 (3·1)
Respiratory, thoracic and mediastinal disorders	6 (21·4)	0	0	6 (21·4)	2 (5·6)	1 (2·8)	2 (5·6)	5 (13·9)	11 (17·2)
Dyspnoea	4 (14·3)	0	0	4 (14·3)	3 (8·3)	0	0	3 (8·3)	7 (10·9)
Respiratory failure	1 (3·6)	0	0	1 (3·6)	0	0	2 (5·6)	2 (5·6)	3 (4·7)
Renal and urinary disorders	5 (17·9)	0	0	5 (17·9)	3 (8·3)	0	0	3 (8·3)	8 (12·5)
Acute renal failure	2 (7·1)	0	0	2 (7·1)	1 (2·8)	0	0	0	2 (3·1)
General disorders and administration site conditions	3 (10·7)	1 (3·6)	3 (10·7)	7 (25·0)	13 (36·1)	1 (2·8)	3 (8·3)	17 (47·2)	24 (37·5)
Fatigue	0	0	0	0	2 (5·6)	0	0	2 (5·6)	2 (3·1)
General physical health deterioration	1 (3·6)	1 (3·6)	1 (3·6)	3 (10·7)	3 (8·3)	1 (2·8)	1 (2·8)	5 (13·9)	8 (12·5)
Mucosal inflammation	0	0	0	0	2 (5·6)	0	0	2 (5·6)	2 (3·1)
Multi-organ failure	0	0	1 (3·6)	1 (3·6)	0	0	2 (5·6)	2 (5·6)	3 (4·7)
Pyrexia	2 (7·1)	0	0	2 (7·1)	4 (11·1)	0	0	4 (11·1)	6 (9·4)
Investigations	8 (28·6)	0	0	8 (28·6)	7 (19·4)	4 (11·1)	0	11 (30·6)	19 (29·7)
Blood bilirubin increased	0	0	0	0	0	2 (5·6)	0	2 (5·6)	2 (3·1)

Blood lactate dehydrogenase increased	1 (3·6)	0	0	1 (3·6)	2 (5·6)	1 (2·8)	0	3 (8·3)	4 (6·3)
Blood potassium decreased	2 (7·1)	0	0	2 (7·1)	2 (5·6)	0	0	2 (5·6)	4 (6·3)
C-reactive protein increased	4 (14·3)	0	0	4 (14·3)	4 (11·1)	1 (2·8)	0	5 (13·9)	9 (14·1)

AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events.

Data are n (%).

*****The CTCAE grade is considered independently for system organ class and for preferred terms.

Supporting Information

Data S1. Methods

Patients

Adult patients with a confirmed diagnosis of AML according to the World Health Organization definition (excluding acute promyelocytic leukaemia) with previously untreated (except hydroxyurea) or relapsed/refractory disease and considered unsuitable for intensive induction or salvage therapy, were eligible for this study.

Inclusion criteria also included life expectancy of ≥3 months and an Eastern Cooperative Oncology Group performance score ≤2, and patients were required to be eligible for low-dose cytarabine treatment and to be considered ineligible for intensive treatment. Patients were excluded if they had aspartate aminotransferase/alanine transaminase >2·5 × upper limit of normal [ULN], international normalized ratio >1.5 × ULN for patients not on therapeutic vitamin K antagonists, bilirubin >1·5 mg/dl, or serum creatinine >2·0 mg/dl. Patients with another malignancy that required treatment, known acute myeloid leukaemia central nervous system involvement, or left ventricular ejection fraction <50% in echocardiography or clinical congestive heart failure New York Heart Association grade III–IV, were also excluded.

A patient's ineligibility for intensive treatment was assessed by the investigator in agreement with the patient, based on a comprehensive documentation of the reasons for this assessment. This documentation included patient age, medical history, performance score, organ dysfunctions, co-morbidities, the patient's informed decision and other relevant factors, supplemented with the investigator's assessment of the reasons for evaluating the patient ineligible for intensive treatment.

Study design

The primary endpoint was to determine the MTD of two BI 811283 schedules in combination with LDAC based on the incidence of DLTs. Further endpoints included incidence and intensity of AEs, PK of cytarabine with BI 811283, and response. Genetic risk group was assessed according to published criteria (Döhner *et al,* 2010).

Patients were randomized to one of two schedules combining BI 811283 (24-hour intravenous infusion) with LDAC (20 mg twice daily subcutaneously, days 1–10 of a 4-week cycle). In Schedule A, patients received BI 811283 on days 1 and 15 of a 4-week cycle. In Schedule B, patients received BI 811283 on day 1 of a 4-week cycle. Dose escalation was conducted for each schedule following a 3+3 design. The starting BI 811283 dose was 5 mg. After the 5 mg dose cohorts, the protocol was amended to escalate the BI 811283 doses to approximately half the highest dose that was considered safe in a concurrent BI 811283 monotherapy trial conducted in solid tumours (Mross *et al,* 2016). Accordingly, the second dose cohorts investigated BI 811283 at a dose of 15 mg per administration in Schedule A, and 40 mg in Schedule B. BI 811283 dosing frequency was chosen based on the expected duration of myelosuppression (Mross *et al,* 2016). The MTD was defined based on the occurrence of DLTs in the first cycle. DLT was defined as drug-related grade ≥3 non-haematologic toxicity (excluding: untreated nausea, untreated vomiting, grade 3 untreated diarrhoea, grade 3 febrile neutropenia and grade 3 infection with grade 3/4 neutropenia). In patients with incomplete haematologic recovery (CRi) or partial remission, persistent Grade 4 neutropenia or thrombocytopenia until 3 weeks after the end of the treatment cycle was also regarded as a DLT, unless the respective Grade 4 cytopenia was pre-existent. In patients who required platelet substitution to maintain a CTCAE Grade < 4 before treatment, a CTCAE Grade 4 thrombocytopenia after treatment did not constitute a DLT.

The study protocol was approved by institutional review boards/ethics committees at participating centres. The study was conducted according to the Declaration of Helsinki guidelines, the International Conference on Harmonization-Good Clinical Practice Guidelines and local legislation. Written informed consent was obtained from all patients (NCT00632749/EudraCT 2007-005684-00/Study 1247.3).

Criteria for therapy continuation

At the end of each treatment cycle, the response to treatment was assessed. To continue treatment with further cycles, the following criteria had to be met: absence of disease progression, neutrophils ≥500/μL (0·5 × 10^9/L) and platelets ≥25,000/μL (25 × 10^9/L), unless Common Terminology Criteria for Adverse Events (CTCAE) grade 4 neutropenia or thrombocytopenia was pre-existing; and acceptable tolerability (in case of a dose-limiting toxicity [DLT], patients could continue therapy only after recovery from DLT to CTCAE levels that would allow further therapy and only with a reduced dose).

Safety assessments

AEs were graded according to Common Terminology Criteria for Adverse Events version 3.0 recording date of onset, end date, treatment/action required and outcome. Safety laboratory examinations included haematology, biochemistry and coagulation parameters. A 12-lead resting electrocardiogram was performed at screening and at end-of-treatment visits.

Efficacy assessments

Response was assessed in the peripheral blood and bone marrow at the end of each treatment cycle. In case of extramedullary manifestations of leukaemia, response assessment by imaging was used to complement the blood and bone marrow assessment. Responses were assessed according to published criteria (Döhner *et al,* 2010).

Pharmacokinetics

Blood was collected at specified time points during the first treatment cycle to determine plasma concentrations of BI 811283 and cytarabine. BI 811283 base salt concentrations were determined by a validated high-performance liquid chromatography tandem mass spectrometry assay (Nuvisan GmbH, Neu-Ulm, Germany). Analysis of the plasma samples for cytarabine was conducted at SGS Cephac Europe, Saint-Benoît Cedex, France.

Statistical analysis

All analyses were descriptive and exploratory by nature.

Table SI. Patient demographic and baseline disease characteristics.

	Schedule A (days 1 and 15 of 4-week cycle) *n* = 28	Schedule B (day 1 of 4-week cycle) *n* = 36	Total *N* = 64
Male/female, *n* (%)	12 (42·9)/16 (57·1)	22 (61·1)/14 (38·9)	34 (53·1)/30 (46·9)
Age, years (median, range)	73 (49–89)	73 (52–83)	73 (49–89)
ECOG performance score, *n* (%)			
0	6 (21·4)	5 (13·9)	11 (17·2)
1	15 (53·6)	22 (61·1)	37 (57·8)
2	7 (25·0)	9 (25·0)	16 (25·0)
Previously untreated, *n* (%)	20 (71·4)	24 (66·7)	44 (68·8)
Relapsed/refractory to prior therapy, *n* (%)	8 (28·6)	12 (33·3)	20 (31·3)
Number of previous anti-cancer therapies (median, range)*	2·5 (1–7)	2·5 (1–7)	2·5 (1–7)
AML considered secondary, *n* (%)	10 (35·7)	15 (41·7)	25 (39·1)
Due to:			
Preceding MDS	8 (80·0)	10 (66·7)	18 (72·0)
Preceding MPN	1 (10·0)	2 (13·3)	3 (12·0)
Prior alkylating agent therapy	1 (10·0)	1 (6·7)	2 (8·0)
Other reason	0	2 (13·3)	2 (8·0)
Genetic risk classification, *n* (%)†			
Adverse	10 (35·7)	12 (33·3)	22 (34·4)
Favourable	1 (3·6)	1 (2·8)	2 (3·1)
Intermediate I	10 (35·7)	10 (27·8)	20 (31·3)
Intermediate II	1 (3·6)	5 (13·9)	6 (9·4)
Missing	6 (21·4)	8 (22·2)	14 (21·9)

AML, acute myeloid leukaemia; ECOG, Eastern Cooperative Oncology Group; MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasms.

*Includes previous therapy for both AML and any other malignancy.

†According to European Leukemia Net criteria (Döhner *et al,* 2010).

Table SII. Incidence of AEs by dose.

	Schedule A (days 1 and 15 of 4-week cycle)					
BI 811283 dose	5 mg (*n* = 4)	15 mg (*n* = 3)	30 mg (*n* = 3)	60 mg (*n* = 4)	100 mg (*n* = 7)	120 mg (*n* = 7)
AE, *n* (%)						
Leukopenia	0	0	1 (33·3)	1 (25·0)	4 (57·1)	5 (71·4)
Anaemia	1 (25·0)	2 (66·7)	1 (33·3)	1 (25·0)	5 (71·4)	5 (71·4)
Dyspnoea	0	1 (33·3)	1 (33·3)	1 (25·0)	2 (28·6)	4 (57·1)

	Schedule B (day 1 of 4-week cycle)							
BI 811283 dose	5 mg (*n* = 4)	40 mg (*n* = 4)	80 mg (*n* = 5)	160 mg (*n* = 3)	240 mg (*n* = 7)	300 mg (*n* = 4)	360 mg (*n* = 3)	420 mg (*n* = 6)
AE, *n* (%)								
Leukopenia	1 (25·0)	1 (25·0)	1 (20·0)	1 (33·3)	3 (42·9)	2 (50·0)	3 (100·0)	2 (33·3)

AE, adverse event.

Table SIII. Best overall response.

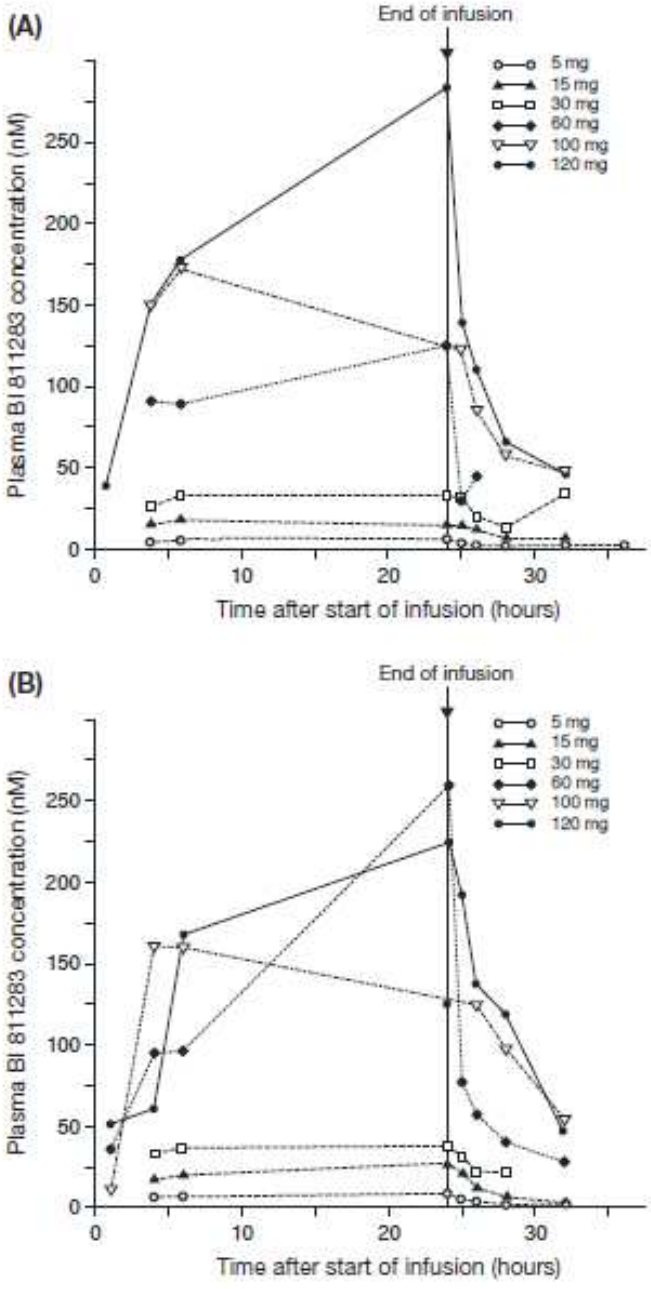
Schedule A (days 1 and 15 of 4-week cycle)							
BI 811283 dose	5 mg (*n* = 4)	15 mg (*n* = 3)	30 mg (*n* = 3)	60 mg (*n* = 4)	100 mg (*n* = 7)	120 mg (*n* = 7)	Total (*N* = 28), n (%)
Best overall response, *n*							
CR	0	0	0	1	0	1	2 (7·1)
CRi	0	0	0	0	0	0	0
PR	0	0	0	0	0	0	0
No change	1	2	1	1	2	3	10 (35·7)
PD	2	1	2	1	4	1	11 (39·3)
Missing	1	0	0	1	1	2*	5 (17·9)

Schedule B (day 1 of 4-week cycle)									
BI 811283 dose	5 mg (*n* = 4)	40 mg (*n* = 4)	80 mg (*n* = 5)	160 mg (*n* = 3)	240 mg (*n* = 7)	300 mg (*n* = 4)	360 mg (*n* = 3)	420 mg (*n* = 6)	Total (*N* = 36), n (%)
Best overall response, n									
CR	1	0	1	1	1	0	1	0	5 (13·9)
CRi	0	0	0	0	0	0	1	0	1 (2·8)
PR	0	1	0	0	0	0	0	0	1 (2·8)
No change	1	2	3	2	4	2	1	2	17 (47·2)
PD	2	0	0	0	2	2	0	2	8 (22·2)
Missing	0	1	1*	0	0	0	0	2	4 (11·1)

CR, complete remission; CRi, complete remission with incomplete hematologic recovery; PR, partial remission; PD, progressive disease.

*One patient not evaluable for response.

Fig S1. Geometric mean plasma concentration–time profiles of BI 811283 during and after the 24-hour infusion of BI 811283. (A) Day 1, cycle 1, Schedule A. (B) Day 15, cycle 1, Schedule A. (C) Day 1, cycle 1, Schedule B.



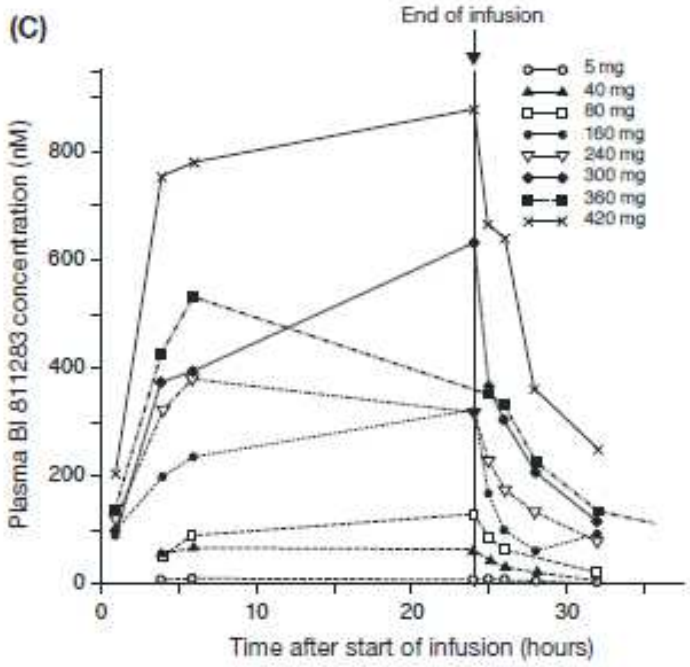

(C)
End of infusion
5 mg
40 mg
80 mg
160 mg
240 mg
300 mg
360 mg
420 mg
Plasma BI 811283 concentration (nM)
800
600
400
200
0
0
10
20
30
Time after start of infusion (hours)

Fig S2. Geometric mean plasma concentration–time profiles of cytarabine. (A) Schedule A. (B) Schedule B.